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(54) Preparation for blood dialysis and method for production thereof.

(57) A preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising (a) solid electrolytes for dialysis, glucose and acetic acid, or (b) solid electrolytes for dialysis, glucose, sodium acetate and acetic acid, and a second composition comprising (a) sodium hydrogen carbonate, or (b) sodium hydrogen carbonate and sodium acetate.

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BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to a preparation for blood dialysis and a method for the production thereof. More particularly, it relates to a uniform powdery preparation for blood dialysis excellent in stability of storage and a method for the production thereof.

Description of the Prior Art:

In the performance of blood dialysis, the partient's blood is purified in the artificial kidney. Inside the artificial kidney, the purification of the blood is effected by keeping the dialytic solution circulated in the artificial kidney, allowing the dialytic solution to contact the blood through the medium of a permeable membrane, and causing the waste matter and water accompanied by the blood to pass into the dialytic solution. The dialytic solution is closely and impartibly related to the improvement of the artificial kidney in performance. The acetate dialytic solution, the leader of the conventional dialytic solutions, is such that owing to the advance of the artificial kidney in quality, the acetic acid allowed to pass from this dialytic solution into the patient's vital organs has gained in quantity and the acetic acid causes the patient to suffer from such displeasing symptoms as headache and hypotension. Thus, it is giving place to the bicarbonate dialytic solution which exerts no appreciable burden upon the patient.

Unlike the acetate dialytic solution, the bicarbonate dialytic solution cannot be prepared as a single-component dope because sodium hydrogen carbonate present therein, on reaction with calcium or magnesium, gives rise to a precipitate. The bicarbonate dialytic solution, therefore, is prepared as a two-component composition comprising sodium hydrogen carbonate (principal solution) and a component containing calcium, magnesium, sodium, etc. (formulating liquid).

The principal component is prepared in the form of powder or solution and the formulating component in the form of solution. The amount of the principal component to be used is in the range of 500 to 1,000 g as powder or 10 to 12 liters as liquid and that of the formulating component in the range of 9 to 12 liters as liquid respectively per patient. In an institute abounding in patients, the work of transferring storage tanks of the dialytic solution exerts a heavy burden on workers. In an institute capable of performing dialysis simultaneously on 20 patients, for example, the dopes of both principal component and formulating component in a total amount enough for 40 patients (about 380 to 480 kg) must be transferred. The institute suffers also from the problem that the transfer and storage of these dopes call for engagement of human labor and require preservation of floor spaces.

In the light of the true state of affairs described above, efforsts are directed to decreasing the weight of the dialytic preparation by producing this preparation in the form of powder. JP-B-58-27,246 (1983), for example, discloses as means for uniform dispersion of a liquid acid a method for producing an electrolytic compound powder of the bicarbonate dialysis quality by powder mixing using a microfine powder of sodium chloride acidified with acetic acid. JP-A-62-30,540 (1987), concerning the production of a preparation for dialysis using sodium acetate as a principal component, discloses a technique for decreasing dispersion of the contents of such microconstituents as $MgCl_2 \cdot 6H_2O$ and $CaCl_2 \cdot 2H_2O$ in the dialytic solution obtained from a dialytic preparation having sodium acetate as a principal component by intimately mixing these microconstituents with sodium acetate and water and converting the resultant mixture into fine powder.

In the powdery preparation for dialysis of the type using sodium hydrogen carbonate as a principal component, calcium chloride and magnesium chloride exhibit a deliquescing property and sodium chloride possibly acquires enhanced hygroscopicity in the presence of calcium chloride and magnesium chloride. This preparation, therefore, undergoes deliquescence or solidification during the course of production, transfer, or storage and entails the disadvantage that it betrays notable dispersion of composition and inferior stability during protracted preservation. Further, since this preparation uses acetic acid as a liquid acid, it possesses a high vapor pressure and readily succumbs to volatilization even when it is adsorbed on an inorganic salt, and lacks stability and workability. In recent years, the practice of curbing possible variation in the blood sugar level by adding glucose to the dialytic solution has been finding acceptance in the field of clinical medicine. None of the preparations heretofore produced dialysis has proved to be capable of retaining stability in protracted preservation.

An object of this invention, therefore, is to provide a novel powdery preparation for dialysis and a method for the production thereof.

Another object of this invention is to provide a powdery preparation for dialysis, which excels in the ability to withstand the impact of transfer and storage and in the maintenance of uniformity and stability of

powder production.

SUMMARY OF THE INVENTION

The objects are accomplished by a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate.

The present invention discloses a preparation for blood dialysis, wherein the liquid acid is acetic acid. The present invention further discloses a preparation for blood dialysis, wherein the acetic acid is specifically adsorbed on granules of the solid sodium acetate-containing electrolytes for dialysis. The present invention further discloses a preparation for blood dialysis, wherein the preparation, on being dissolved in a prescribed amount of water, produces the following components of solid electrolytes for dialysis, glucose, and liquid acid from the first composition:

Na^+	90 to 140 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	6 to 15 mmols
Glucose	4 to 12 mmols

and the following components of sodium hydrogen carbonate from the second composition:

Na^+	15 to 40 mmols
HCO_3^-	15 to 40 mmols

The present invention further discloses a preparation for blood dialysis, wherein the first solid composition for dialysis and a desiccant (moisture absorbent) are contained in a moistureproof packing material having moisture permeability (20 • C) of not more than 2.0 g/cm^2 • 24hrs.

The objects described above are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate.

The present invention discloses a preparation for blood dialysis, wherein the liquid acid is acetic acid, which method is characterized by the fact that the first composition is produced by mixing the components of the solid electrolytes for dialysis and glucose, pulverizing and granulating the resultant mixture, and subsequently mixing the resultant granules with the liquid acid.

These objects are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate.

The present invention discloses a preparation for blood dialysis, wherein the liquid acid is acetic acid, which method is characterized by the fact that the first composition is produced by spraying an aqueous solution of the components of the solid electrolytes for dialysis other than sodium chloride into a fluidized bed of a mixed powder of sodifum chloride and glucose and, at the same time, granulating the wet mixed powder, and mixing the resultant granules with the liquid acid.

These objects are further accomplished by a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid and a second powdery composition comprising sodium hydrogen carbonate and sodium acetate.

The present invention further discloses a preparation for blood dialysis, wherein the preparation on being dissolved in a prescribed amount of water produces the following components of solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid from the first composition:

Na^+	85 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

and the following components of sodium hydrogen carbonate and sodium acetate from the second composition:

Na^+	15 to 40 mmols
HCO_3^-	15 to 40 mmols
CH_3COO^-	0.5 to 3 mmols

The present invention further discloses a preparation for blood dialysis, wherein the second composition contains sodium chloride.

The present invention further discloses a preparation for blood dialysis, wherein the preparation on being dissolved in a prescribed amount of water produces the following components of solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid from the first composition:

Na^+	6 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	4 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

and the following components of sodium hydrogen carbonate, sodium acetate, and sodium chloride from the second composition:

Na^+	15 to 135 mmols
Cl^-	1 to 120 mmols
HCO_3^-	15 to 40 mmols
CH_3COO^-	0.5 to 3 mmols

The objects described above are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid and a second powdery composition comprising sodium hydrogen carbonate and sodium acetate, which method is characterized by the fact that the first composition is produced by mixing the components of the solid inorganic salts for dialysis, sodium acetate, and glucose, pulverizing and then granulating the resultant mixture, and mixing the resultant granules with acetic acid.

These objects are further accomplished by a method for the production of a preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid and a second powdery composition comprising sodium hydrogen carbonate and sodium acetate, which method is characterized by the fact that the first composition is produced by spraying an aqueous solution of the components of the solid inorganic salts for dialysis excluding sodium chloride and containing or not containing sodium acetate into a fluidized bed of a mixed powder consisting of sodium chloride and glucose and not containing or containing sodium acetate and, at the same time, granulating the wet mixed powder, and mixing the resultant granules with acetic acid.

Further, the present invention discloses a method for the production of a preparation for blood dialysis, wherein the second composition is produced by mixing sodium acetate powder or mixed powder of sodium

acetate and sodium chloride with sodium hydrogen carbonate and subsequently granulating the resultant mixture.

EXPLANATION OF THE PREFERRED EMBODIMENT

The preparation for blood dialysis according with the present invention comprises two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate.

The solid electrolytes for dialysis which are usable for the first composition include sodium chloride, potassium chloride, calcium chloride magnesium chloride, and sodium acetate, for example. The liquid acid is used as a pH-adjusting agent. The liquid acids which are usable for this purpose include acetic acid, lactic acid, and hydrochloric acid, for example. Among other liquid acids mentioned above, acetic acid proves to be particularly desirable. This acetic acid is generally adsorbed specifically by the granules of the solid electrolyte for dialysis, particularly by the sodium acetate contained in the granules.

The first composition is preferable, on being dissolved in a prescribed amount of water, to produce the following components of solid electrolytes for dialysis and liquid acid:

Na^+	90 to 140 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	6 to 15 mmols
Glucose	4 to 12 mmols

preferably:

Na^+	100 to 130 mmols
K^+	1.5 to 3 mmols
Ca^{++}	0.75 to 1.8 mmols
Mg^{++}	0.3 to 0.8 mmol
Cl^-	100 to 130 mmols
CH_3COO^-	8 to 12 mmols
Glucose	6 to 10 mmols

The average particle size of the first composition is in the range of 10 to 200 mesh, preferably 14 to 100 mesh, of standard sieves.

The first composition is desired to be produced by either the dry method or the fluidized-bed method.

By the dry method, the first composition is obtained by stirring and mixing the solid electrolytes for dialysis and glucose with a stirring and mixing device such as a vertical granulator, for example, then pulverizing the mixed solid electrolytes with a pulverizing device such as a pin mill mixing the pulverized solid electrolytes with a stirring and mixing device such as a vertical granulator, for example, granulating the resultant mixture with a dry granulating device such as a roller compacter, for example, combining the resultant granules with the liquid acid, and mixing them with a stirring and mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer, for example.

By the fluidized-bed method, the first composition is obtained by dissolving the solid electrolytes for dialysis other than sodium chloride in water of an amount 0.8 to 30 times, preferably 1.5 to 15 times, the amount of the solid electrolytes, spraying the resultant aqueous solution into a fluidized bed from of a mixed powder of sodium chloride and glucose powder inside a fluidized-bed granulating device and, at the same time, granulating the wet powder, combining the resultant granules with the liquid acid, and mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer, for example. The mixed powder of sodium chloride and glucose is obtained, for example, by mixing them with a stirring and mixing device such as a vertical granulator a Nauter mixed.

The second composition is a powder comprising sodium hydrogen carbonate. When this second composition is dissolved in a prescribed amount of water, the sodium hydrogen carbonate produces 15 to 40 mmols of Na^+ and 15 to 40 mmols of HCO_3^-, preferably 20 to 30 mmols of Na^+ and 20 to 30 mmols of

HCO_3^-. The average particle size of the second composition is not more than 500 μm, preferably in the range of 200 to 10 μm.

The first and second compositions which are produced as described above are placed in separate containers. Prior to use, these compositions are dissolved in water and the resultant aqueous solution is supplied to the artificial kidney, there to be used as a liquid for blood dialysis.

The packing material to be used for containing these compositions is as already described. The first and second compositions are preferable to be each contained in a packing material in combination with an air-permeable container filled with a desiccator such as silica gel, a synthetic zeolite type moisture absorbent, or a calcium carbonate type moisture absorbent.

Another preparation for blood dialysis according with the present invention comprises two compositions, i.e. a first powdery composition comprising solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid and a second composition comprising sodium hydrogen carbonate and sodium acetate.

The solid inorganic salts for dialysis which are used in the first composition are preferable to be readily soluble in water. The solid inorganic salts which fulfil this requirement include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and sodium acetate, for example.

When the first composition is dissolved in a prescribed amount of water, the solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid are preferable to produce the following components:

Na^+	85 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

preferably

Na^+	95 to 125 mmols
K^+	1.5 to 3 mmols
Ca^{++}	0.75 to 1.8 mmols
Mg^{++}	0.3 to 0.8 mmol
Cl^-	100 to 130 mmols
CH_3COO^-	5 to 9 mmols
Glucose	6 to 10 mmols

Where the second composition is used in combination with a sodium chloride-containing composition as described specifically herein below, the first composition is such that when it is dissolved in a prescribed amount of water, the solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid are preferable to produce the following components:

Na^+	6 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	4 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

preferably

Na^+	30 to 100 mmols
K^+	1.5 to 3 mmols
Ca^{++}	0.75 to 1.8 mmols
Mg^{++}	0.3 to 0.8 mmol
Cl^-	100 to 130 mmols
CH_3COO^-	5 to 9 mmols
Glucose	6 to 10 mmols

The average particle size of the first composition is in the range of 10 to 200 mesh, preferably 14 to 100 mesh, of standard sieves.

The first composition is preferable to be produced by either the dry method or the fluidized-bed method.

By the dry method, the first composition is obtained by stirring and mixing the solid inorganic salts for dialysis and sodium acetate with a stirring and mixing device such as a vertical granulator, for example, then pulverizing the mixed solid electrolytes with a pulverizing device such as a pin mill, mixing the pulverized solid electrolytes with a stirring and mixing device such as a vertical granulator, for example, granulating the resultant mixture with a dry granulating device such as a roller compacter, for example, combining the resultant granules with acetic acid, and mixing them with a stirring and mixing device such as a vertical granulator or a Nauter mixer, for example.

By the fluidized-bed method, the first composition is obtained by dissolving the solid inorganic salts for dialysis other than sodium chloride in water of an amount 0.8 to 30 times, preferably 1.5 to 15 times, the amount of the solid inorganic salts, spraying the resultant aqueous solution into a fluidized bed formed of a mixed powder of sodium chloride and glucose inside a fluidized-bed granulating device and, at the same time, granulating the wet powder, combining the resultant granules with acetic acid, and mixing them with a stirring and and mixing device such as a vertical granulator or a Nauter mixer, for example. In this case, sodium acetate may be incorporated into the aqueous solution, into the mixed powder of sodium chloride and glucose, or to both of them.

The second composition is a powdery composition comprising sodium hydrogen carbonate and sodium acetate. When this second composition is dissolved in a prescribed amount of water, the components thereof, i.e. sodium hydrogen carbonate and sodium acetate, produce 15 to 40 mmols of Na^+, 15 to 40 mmols of HCO_3^-, and 0.5 to 3 mmols of CH_3COO^-, preferably 18 to 32 mmols of Na^+, 18 to 35 mmols of HCO_3^-, and 0.8 to 2.5 mmols of CH_3COO^-. Where the second composition additionally incorporates therein sodium chloride, it is preferable to be such that when the composition is dissolved in a prescribed amount of water, the components thereof, i.e. sodium hydrogen carbonate, sodium acetate, and sodium chloride, produce 15 to 135 mmols of Na^+, 1 to 120 mmols of Cl^-, 15 to 40 mmols of HCO_3^-, and 0.5 to 3 mmols of CH_3COO^-, preferably 40 to 120 mmols of Na^+, 35 to 115 mmols of Cl^-, 20 to 35 mmols of HCO_3^-, and 0.8 to 2.5 mmols of CH_3COO^-.

The second composition is obtained by mixing sodium acetate powder or a mixed powder of sodium acetate and sodium chloride with sodium hydrogen carbonate powder within a mixing device such as a vertical granulator and then granulating the resultant mixture in a dry granulating device such as a roller compacter.

The first and second compositions which are produced as described above are placed in separate containers. Prior to use, these compositions are dissolved in water and the resultant aqueous solution is supplied to the artificial kidney, there to be used as a liquid for blood dialysis.

The packing material to be used for containing these compositions is preferable to possess low moisture permeability. It is preferable, for example, to use a moistureproof packing material possessing moisture permeability (20 • C) of not more than 2.0 $g/m^2 \cdot 24hrs$. As one packing material fulfilling this requirement, there may be cited a laminate film which is obtained by superposing polyethylene terephthalate/polyethylene/aluminum foil/polyethylene layers measuring 12 μm, 15 μm, 7 μm, and 30 μm respectively in thickness (moisture permeability 0.1 $g/m^2 \cdot 24hrs$.

Now, the present invention will be described more specifically below with reference to working examples. Wherever the term "parts" is used in the working examples, it is meant as "parts by weight" unless otherwise specified.

Example 1

In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product code of "VG-25P"), 2188.7 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], 35.6 parts of magnesium chloride [$MgCl_2 \cdot 6H_2O$], 215.3 parts of sodium acetate [$CH_3COONa \cdot 3H_2O$], and 525 parts of glucose were mixed by stirring. Then, the resultant mixture was pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z"), and further mixed by stirring with the vertical granulator. The resultant mixture was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 patts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	7.79
12-32	51.41
32-48	6.70
48-80	3.56
80-150	2.75
150-	27.82
Average particle diameter	12-32 meshes

Separately, powdery sodium hydrogen carbonate was prepared as the second composition.

Example 2

An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], 35.6 parts of magnesium chloride [$MgCl_2 \cdot 6H_2O$], 357.2 parts of sodium acetate [$CH_3COONa \cdot 3H_2O$] in water of an amount 5 times the amount of the inorganic salts. Separately, granules obtained by mixing by stirring 2188.7 parts of sodium chloride and 525 parts of glucose with the vertical granulator were fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15") and the fluidized bed of the granules was sprayed with the aforementioned aqueous solution to gain in weight. The granules thus obtained were placed in the vertical granulator and were then mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	1.20
12-32	10.23
32-48	17.21
48-80	40.32
80-150	26.87
150-	4.17
Average particle diameter	40-80 meshes

Separately, powdery sodium hydrogen carbonate was prepared as the second composition.

Example 3

The first composition obtained in Example 2 was placed in combination with silica gel as a desiccant in a bag made of a laminate film obtained by superposing polyethylene terephthalate (12 μm), polyethylene (15 μm), aluminum foil (7 μm), and polyethylene (30 μm) layers and tested for stability in storage at 40 °C. The results were as shown in Table 1.

Table 1

Item	0 month	1 month	2 months
Color difference (ΔE)	0.00	0.52	0.92
Residual ratio of acetic acid ion (%)	100.0	98.9	98.9
Occurrence of aggregation		No	No

Example 4

The first composition obtained in Example 1, a composition produced by following the procedure of Example 1 except that the addition of sodium acetate was omitted (composition of Control 1), and a mixture of 2188.7 parts of sodium chloride and 41.5 g of acetic acid (composition of Control 2) were left standing in the open air at 30 • C for 30 minutes and then tested for residual ratio of acetic acid. The results were as shown in Table 2.

Table 2

Time	Composition of		
	Example 1	Control 1	Control 2
Immediately after production	100%	100%	100%
After 30 minutes following production	100.2%	17.6%	12.7%

It is clearly noted from Table 6 that the preparations for blood dialysis according with the present invention show specific adsorption of acetic acid by sodium acetate and excel in stability in preservation.

Example 5

In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product code of "VG-25P"), 2188.7 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], 35.6 parts of magnesium chloride [$MgCl_2 \cdot 6H_2O$], 175.3 parts of sodium acetate, and 521.5 parts of glucose were mixed by stirring. Then, the resultant mixture was pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z") and the resultant powder was mixed by stirring with the vertical granulator. The resultant mixture was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 parts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	0.20
12-32	47.11
32-48	16.35
48-80	7.29
80-150	5.38
150-	23.17

Example 6

An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], 175.3 parts of sodium acetate, and 35.6 parts of magnesium chloride [$MgCl_2 \cdot 6H_2O$] in 1500 parts of water (about 3 times the amount of the electrolytes). Separately, 2188.7 parts of sodium

chloride and 525 parts of glucose were mixed by stirring with the vertical granulator. The resultant mixture was fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15"). The fluidized bed of the powder was sprayed with the aforementioned aqueous solution to gain in weight. The granules thus obtained placed in the vertical granulator and mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	0.82
12-32	8.78
32-48	15.57
48-80	44.14
80-150	25.74
150-	4.76

Example 7

A mixed powder comprising of 750 parts of sodium hydrogen carbonate and 40.0 parts of sodium acetate [$CH_3COONa \cdot 3H_2O$] was mixed by stirring with the vertical granulator. The resultant mixture was pelletized with a roller compacter. The second composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	6.23
12-32	30.11
32-48	15.87
48-80	10.69
80-150	4.80
150-	32.30

Example 8

The first and second compositions obtained in Examples 6 and 7 were separately placed, as not accompanied by any desiccator, in bags made of a laminate film obtained by superposing polyethylene terephthalate (12 μm), polyethylene (15 μm), aluminum foil (7 μm), and polyethylene (30 μm) layers and tested for stability in storage at 40 • C. The results were as shown in Table 3.

Table 3

Item	0 month	1 month	2 months
First composition			
Color difference (ΔE)	0.00	0.05	0.11
Residual ratio of acetic acid ion (%)	100.0	99.9	99.7
Occurrence of aggregation		No	No
Second composition			
Color difference (ΔE)	0.00	0.03	0.05
Occurrence of aggregation		No	No

The "color difference (ΔE)" represents the numerical value (absolute number) determined by the use of a colorimetric system (produced by Minolta Camera K.K. and marketed under product code of "CD-200").

The "residual ratio of acetic acid ion" represents the magnitude determined by dissolving part of a sample in water and examining the resultant aqueous solution by high-speed liquid chromatography (by the use of a system produced by Nippon Bunko K.K. and marketed under product code of "BIP-I").

Example 9

In a vertical granulator (stirring and mixing device produced by Fuji Sangyo K.K. and marketed under product code of "VG-25P"), 1038.6 parts of sodium chloride, 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], 35.6 parts of magnesium chloride [$MgCl_2 \cdot 6H_2O$], 175.3 parts of sodium acetate ($CH_3COONa \cdot 3H_2O$], and 525 parts of glucose were mixed by stirring. The resultant mixture was then pulverized with a pin mill (pulverizing device produced by Fuji Sangyo K.K. and marketed under trademark designation of "Kollplex 16Z"). The resultant powder was further mixed by stirring with the vertical granulator. The mixture consequently obtained was pelletized with a roller compacter (dry granulating device produced by Turbo Kogyo K.K. and marketed under product code of "WP-160X60"). The granules and 41.5 parts of acetic acid added thereto were mixed by stirring with the vertical granulator. The first composition obtained as the result was found to have a particle size distribution as follows.

Mesh	%
-12	3.25
12-32	24.38
32-48	26.71
48-80	9.21
80-150	5.51
150-	30.94

Example 10

An aqueous solution was obtained by dissolving 52.2 parts of potassium chloride, 77.2 parts of calcium chloride [$CaCl_2 \cdot 2H_2O$], and 290.8 parts of sodium acetate [$CH_3COONa \cdot 3H_2O$] in 1500 parts of water. Separately, 1038.6 parts of sodium chloride and 525 parts of glucose were mixed by stirring with the vertical granulator. The resultant mixture was fluidized within a fluidized-bed pelletizer (produced by Fuji Sangyo K.K. and marketed under product code of "STREA-15"). The fluidized bed of the powder was sprayed with the aforementioned aqueous solution to gain in weight. The granules obtained as described above were placed in the vertical granulator and were mixed by stirring with 41.5 parts of acetic acid added thereto. The first composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	2.37
12-32	9.36
32-48	16.81
48-80	43.44
80-150	23.98
150-	4.04

Example 11

A mixed powder comprising of 750 parts of sodium hydrogen carbonate, 40.4 parts of sodium acetate [$CH_3COONa \cdot 3H_2O$], and 1150.0 parts of sodium chloride was mixed by stirring with the vertical granulator. The resultant mixture was pelletized with the roller compacter. The second composition consequently obtained was found to have a particle size distribution as follows.

Mesh	%
-12	7.12
12-32	32.48
32-48	20.77
48-80	7.51
80-150	4.53
150-	27.59

Control 3

A first composition obtained by following the procedure of Example 6 except that the addition of sodium acetate was omitted and a second composition obtained by following the procedure of Example 7 except that the amount of sodium acetate added was changed to 215.3 parts were separately placed in the same packing material as used in Example 8 and tested for stability in storage at 40°C. The results were as shown in Table 4.

It is clearly noted from Table 4 that the compositions according with the present invention excelled those of Control 3 in terms of coloration, aggregation, and residual ratio of acetic acid ion.

Table 4

Item	0 month	1 month	2 months
First composition			
Color difference (ΔE)	0.00	0.69	2.07
Residual ratio of acetic acid ion (%)	100.0	87.6	76.5
Occurrence of aggregation		Yes	Yes
Second composition			
Color difference (ΔE)	0.00	0.07	0.19
Occurrence of aggregation		Yes	Yes

The "color difference (ΔE)" represents the numerical value (absolute number) determined by the use of a colorimetric system (produced by Minolta Camera K.K. and marketed under product code of "CD-200"). The "residual ratio of acetic acid ion" represents the magnitude determined by dissolving part of a sample in water and examining the resultant aqueous solution by high-speed liquid chromatography (by the use of a system produced by Nippon Bunko K.K. and marketed under product code of "BIP-I").

The preparation for blood dialysis according with the present invention is extremely light as compared with the conventional dialytic solution because it comprises two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate. When acetic acid is used as the liquid acid meant as a pH-adjusting agent, the preparation enjoys the advantage that it exhibits highly satisfactory stability in protracted preservation because the acetic acid is specifically adsorbed by the sodium acetate in the solid electrolytes.

Further, since the preparation for blood dialysis contained in combination with a desiccant in a moistureproof packing material, it has the advantage that it is retained very stably in the state of low moisture.

Further, another preparation for blood dialysis according with the present invention comprises two compositions, i.e. a first powdery composition comprising solid inorganic salts for dialysis, glucose, sodium acetate, and acetic acid and a second powdery composition comprising sodium hydrogen carbonate and sodium acetate, and is extremely light as compared with the conventional dialytic solution. This preparation further enjoys the advantage that it exhibits highly satisfactory stability in protracted storage and excels in the ease of use because acetic acid is used as the liquid acid meant as a pH-adjusting agent and is allowed to impregnate the solid inorganic salt particles containing the aforementioned acetate.

It has been found incredibly that the stability of the preparation is invariably high when sodium chloride is incorporated in the first composition or in the second composition. This freedom as to the incorporation of

the sodium chloride allows the contents of sodium chloride in the first composition and the second composition to approximate to each other to the greatest possible extent and obviates the necessity for using different devices in dissolving the two compositions of the preparation. Thus, the prevent invention contributes to simplifying the equipment required in putting the preparation to use.

The preparation for blood dialysis according with the present invention is produced by the dry method or the fluidized-bed method. In spite of the use of calcium chloride or magnesium chloride, a substance which has heretofore defied uniform pulverization because of an excessively high deliquescing property, the powdery compositions of the preparation can be homogenized. Further, the problem that the components of the compositions cannot be easily distributed uniformly can be precluded by the aforementioned method of production.

Claims

1. A preparation for blood dialysis comprising two compositions, i.e. a first powdery composition comprising solid electrolytes for dialysis, glucose, and a liquid acid and a second powdery composition comprising sodium hydrogen carbonate.

2. A preparation according to claim 1, wherein said liquid acid is acetic acid.

3. A preparation according to claim 2, wherein said acetic acid is specifically adsorbed by granules of said solid electrolytes for dialysis containing sodium acetate.

4. A preparation according to one of claims 2 and 3, which on being dissolved in a prescribed amount of water produces the following components of solid electrolytes for dialysis, glucose, and acetic acid from said first composition :

Na^+	90 to 140 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	6 to 15 mmols
Glucose	4 to 12 mmols

and the following components of said sodium hydrogen carbonate from said second composition :

Na^+	15 to 40 mmols
HCO_3^-	15 to 40 mmols.

5. A preparation according to any one of claims 1 - 4, wherein said first composition is contained, together with a dessicant, in a moistureproof packing material having moisture permeability (20 • C) of not more than 2.0 $g/cm^2 \cdot 24hrs$.

6. A method for the production of a preparation for blood dialysis as defined in claim 2, which method comprises preparing said first composition by mixing the components of said solid electrolytes for dialysis and glucose, pulverizing and then granulating the resultant mixture, and then mixing the resultant granules with acetic acid.

7. A method for the production of a preparation for blood dialysis as defined in claim 2, which method comprises preparing said first composition by spraying an aqueous solution of the components of said solid electrolytes for dialysis other than sodium chloride into a fluidized bed of the mixed powder of sodium chloride and glucose and, at the same time, granulating the wet mixed powder, and mixing the resultant granules with acetic acid.

8. A preparation for blood dialysis according to claim 2, wherein said first powdery composition and said second powdery composition further comprise sodium acetate.

9. A preparation according to claim 8, which on being dissolved in a prescribed amount of water produces the following components of said solid electrolytes for dialysis, glucose, sodium acetate, and acetic acid from said first composition :

Na^+	85 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	90 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

and the following components of sodium hydrogen carbonate and sodium acetate from said second composition :

Na^+	15 to 40 mmols
HCO_3^-	15 to 40 mmols
CH_3COO^-	0.5 to 3 mmols.

10. A preparation according to claim 8, wherein said second composition further comprises sodium chloride.

11. A preparation according to claim 10, which on being dissolved in a prescribed amount of water produces the following components of said solid electrolytes for dialysis, glucose, sodium acetate, and acetic acid from said first composition :

Na^+	6 to 135 mmols
K^+	0 to 4 mmols
Ca^{++}	0.5 to 2.2 mmols
Mg^{++}	0.2 to 1.0 mmol
Cl^-	4 to 140 mmols
CH_3COO^-	4 to 10 mmols
Glucose	4 to 12 mmols

and the following components of sodium hydrogen carbonate, sodium acetate, and sodium chloride from said second composition :

Na^+	15 to 135 mmols
Cl^-	1 to 120 mmols
HCO_3^-	15 to 40 mmols
CH_3COO^-	0.5 to 3 mmols.

12. A method for the production of a preparation for blood dialysis as defined in claim 8, which method comprises preparing said first composition by mixing the components of said solid electrolytes for dialysis, sodium acetate, and glucose, pulverizing and then granulating the resultant mixture, and subsequently mixing the resultant granules with acetic acid.

13. A method for the production of a preparation for blood dialysis as defined in claim 8, which method comprises preparing said first composition by spraying an aqueous solution of the components of said

solid electrolytes for dialysis excluding sodium chloride and containing or not containing sodium acetate into a fluidized bed of a mixed powder of sodium chloride and glucose and, at the same time, granulating the wet mixed powder and mixing the resultant granules with acetic acid.

14. A method according to claim 12 or claim 13, wherein said second composition is obtained by mixing sodium acetate powder or a mixed powder of sodium acetate and sodium chloride with sodium hydrogen carbonate and thereafter granulating the resultant mixture.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 10 2866

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
Y	EP-A-0 034 916 (VELTMAN) * page 58, line 7 - line 22 * * page 63 - page 71; claims 1-10; figures 1,4; examples 6,7 *	1-14	A61M1/16 A61K9/08
Y	EP-A-0 177 614 (TOMITA PHARMACEUTICAL CORP.) * page 10, line 18 - page 15, line 2; claims 1-8 *	1-14	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

A61M
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 March 1994	Michels, N

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/001517

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K33/14, 31/7004, 9/14, A61P7/08, A61J3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K33/14, 31/7004, 9/14, A61P7/08, A61J3/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY(STN), CAPLUS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-178802 A (Tomita Pharmaceutical Co., Ltd.), 28 June, 1994 (28.06.94), Full text & EP 602921 A1 & US 5540842 A	1-10
A	JP 2000-026280 A (Nissho Corp.), 25 January, 2000 (25.01.00), Full text (Family: none)	1-10
A	JP 2002-291878 A (Shimizu Pharmaceutical Co., Ltd.), 08 October, 2002 (08.10.02), Full text (Family: none)	1-10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March, 2005 (29.03.05)	12 April, 2005 (12.04.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/001517

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 11-114054 A (Nikkiso Co., Ltd.), 27 April, 1999 (27.04.99), Full text; particularly, example 2 (Family: none)	1-10

PHARMACEUTICAL FOR HEMODIALYSIS AND ITS PRODUCTION

Publication number: JP2311418
Publication date: 1990-12-27
Inventor: WATANABE TOMIO; KOYAMA SAWAKO; KAWAHARA KAZUO; WATANABE EIJI; UMEKI TATEAKI
Applicant: TERUMO CORP
Classification:
- international: *A61K33/00; A61K33/14*; A61K33/00; A61K33/14; (IPC1-7): A61K33/00
- european:
Application number: JP19890134339 19890526
Priority number(s): JP19890134339 19890526

Abstract of **JP2311418**

PURPOSE:To obtain the subject pharmaceutical, composed of a powdery composition composed of a dialytic solid electrolyte and liquid acid and a powdery composition composed of sodium hydrogencarbonate and glucose, excellent in transportation and preservation of its initial quality and good in maintenance and stability of homogeneity in producing powder. CONSTITUTION:A pharmaceutical obtained by combining (A) the first composition prepared by granulating sodium chloride powder in a fluidized bed while spraying an aqueous solution of respective ingredients of a dialytic solid electrolyte other than the sodium chloride on the sodium chloride powder or mixing the respective ingredients of the dialytic solid electrolyte, pulverizing the resultant mixture, then granulating the obtained powder and blending a liquid acid (preferably acetic acid) with the formed granulated substance with (B) the second composition obtained by mixing powder of glucose with sodium hydrogencarbonate and subsequently granulating the formed mixture. The concentrations of the respective ingredients (A) and (B) are within the ranges shown in Tables 1 and 2 when dissolved in a prescribed amount of water and the respective ingredients are placed in a moistureproof packaging material having <=2.0m<2>.24hr moisture permeability (at 20 deg.C) and then contained together with a drying agent, such as a moisture absorbent, therein.

PHARMACEUTICAL FOR HEMODIALYSIS AND ITS PRODUCTION

Publication number: JP2311419
Publication date: 1990-12-27
Inventor: WATANABE TOMIO; KOYAMA SAWAKO; KAWAHARA KAZUO; WATANABE EIJI
Applicant: TERUMO CORP
Classification:
- International: *A61K33/00; A61K33/14;* A61K33/00; A61K33/14; (IPC1-7): A61K33/00
- european:
Application number: JP19890134340 19890526
Priority number(s): JP19890134340 19890526

Abstract of **JP2311419**

PURPOSE:To obtain the subject pharmaceutical, composed of a powdery composition composed of a dialytic solid electrolyte, glucose and liquid acid and a powdery composition composed of sodium hydrogencarbonate, excellent in transportation and preservation its initial quality and good in maintenance and stability of homogeneity in producing powder. CONSTITUTION:A pharmaceutical obtained by combining (A) the first composition prepared by mixing respective ingredients of a dialytic solid electrolyte with glucose, pulverizing the resultant mixture and then granulating the obtained powder or granulating mixed powder of sodium chloride and glucose in a fluidized bed while spraying an aqueous solution of the dialytic solid electrolyte other than the sodium chloride thereon and blending the resultant granulated substance with a liquid acid (preferably acetic acid) with (B) the second powdery composition composed of sodium hydrogencarbonate. The concentrations of the respective ingredients (A) and (B) are within the ranges shown in Tables 1 and 2 and the aforementioned ingredients, together with a drying agent, are respectively contained in a moistureproof packaging material having <=2.0g/m<2>.24hr moisture permeability (at 20 deg.C).

PREPARATION FOR BLOOD DIALYSIS AND ITS PRODUCTION

Publication number: JP3038527
Publication date: 1991-02-19
Inventor: WATANABE TOMIO; KOYAMA SAWAKO; KAWAHARA KAZUO; WATANABE EIJI
Applicant: TERUMO CORP
Classification:
- international: *A61K33/00*; A61K33/00; (IPC1-7): A61K33/00
- european:
Application number: JP19890173120 19890706
Priority number(s): JP19890173120 19890706

Abstract of **JP3038527**

PURPOSE:To obtain the subject preparation consisting of a powdery composition consisting of a solid inorganic salt for dialysis, saccharide, glucose, sodium acetate and acetic acid and powdery composition consisting of sodium hydrogen carbonate and sodium acetate and having excellent storage stability and good handling properties. CONSTITUTION:(A) The preparation consisting of the first powdery composition containing a solid inorganic salt for dialysis, glucose, sodium acetate and acetic acid at a ratio of Na<+> of 85-135mm mol, K<+> of 0-4mm mol, Ca<+> of 0.5-2.2mm mol, Mg<++> of 0.2-1.0mm mol, Cl<-> of 90-14-mm mol, CH3COO<-> of 4-10mm mol; glucose of 4-12mm mol when dissolve in a definite amount of water and (B) the second powdery composition containing sodium hydrogen carbonate and sodium acetate at a ratio of Na<+> of 15-40mm mol, HCO of 15-40mm mol and CH3COO<-> of 0.5-3mm mol when dissolved in a definite amount of water.